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Directions and Challenges in Health Sciences Research

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I want to tell you first of all how pleased I am to be in North Carolina again. Although it is now more than six months since I moved to Bethesda, this area is still home to me. I am delighted to be here as Director of the National Institutes of Health to participate in the dedication of this magnificent facility—the first true home of the National Institute of Environmental Health Sciences since it was established 16 years ago this month—and to launch today's science program in which the achievements of NIEHS scientists will be presented.

This is a singular occasion for me—a coming together with members of both of my NIH and university families to talk about the great humanitarian adventure of which we are a part. This is an exquisitely exciting time in biomedical research and I am happy to be a part of the process of promoting its well-being and of ensuring that its findings contribute to the health of people here and around the world.

The new campus of the National Institute of Environmental Health Sciences is an especially appropriate place in which to discuss directions and challenges in health sciences research. Brought together here at "The Park" is a diverse collection of outstanding talent, dedicated to the task of unravelling the mysteries of environmental impacts upon biological systems, so that we may all live more congenially in the air and soil and sea around us. The difficulty of the task is exceeded only by its importance. Ours is a job that will never be completed—but that is part of its fascination.

I view this Institute and its focus on the environmental health sciences as a symbol of the rounding out of the biomedical research armamentarium of the NIH. This concept was summarized by my predecessor, Donald S. Fredrickson, who told a congressional committee some years ago that there are three great generic categories of inquiry in biomedical science. One, he said, is to understand biological systems. Another is to understand how the genetic code determines the fitness of individuals in regard to the functioning of their biological systems. The third, Fredrickson said (*1*),

> ". . . is a question of how man and other animals adapt to the environment and ecology in which they live, and that adaptation is dependent both on the nature of the environment and on the genetic structure. . . ."

All three categories of inquiry are now being vigorously pursued by the National Institutes of Health. While the work of all 11 of our Institutes is a collaborative effort that intermingles at many levels, it is the specific charge of NIEHS to link the biological processes with the world around us. The study of the interaction is a huge task, and a vital one, if we are progressively to break down the barriers to prevention and cure of the chronic and degenerative illnesses that presently seem so formidable.

This Institute draws upon the knowledge base of NIH as a whole in pursuing its mission. In that sense, it exemplifies the broad reach of the entire agency. It conducts and supports research to develop new knowledge germane to the processes by which human health can be adversely affected by the environment. This involves a broad spectrum of disciplines and approaches, ranging from basic studies of molecular and cell biology to research associated with the detection of hazardous chemicals, and with the extrapolation of laboratory data to man, and the estimation of risks of human exposure.

For example, through his chairmanship of the National Toxicology Program, Dr. Rall leads a Departmental effort to strengthen the science base in toxicology, to test potentially toxic chemi-

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cals, and to develop more sensitive and rapid methods for testing toxicity. The program helps to avoid duplication of effort and provides a vehicle for setting priorities among chemicals of concern. The information developed through NIEHS is essential in designing effective disease prevention strategies. This Institute has identified prevention of environmentally related diseases as a major priority. In this fiscal year (1983), for example, the Institute expects to devote approximately 90% of its budget to activities considered disease prevention.

The mechanisms by which environmental agents contribute to chronic and degenerative diseases remain poorly understood. Nevertheless, there is no question that the environment—man-made and natural—is a major factor in disease and disability. I am personally persuaded that the relationship is greater than has heretofore been appreciated. Recent findings point increasingly toward the causal importance of dietary, occupational, industrial, and other environmental factors in several of the major diseases of today. Many of these factors result from activities that are subject to human control. Many are by-products of modern technology and, therefore, require continuous balancing of social benefits against health risks by policymakers in our government. We cannot achieve a zero-risk society, but it is appropriate that the people themselves, through their elected representatives, decide which risks are worth taking.

I have described NIEHS as a symbol of the broad, integrated approach to the pursuit of biomedical knowledge and the conquest of disease that is followed by NIH as a whole. There is another vital aspect of this approach that must also be emphasized; that is, the larger community of effort that translates new knowledge into medical practice and measures for health maintenance.

The makeup of this larger scientific research community underscores the fact that there is no Federal monopoly on health research. We include in the research communtiy, laboratories at publicly supported and private colleges, universities, academic health centers and teaching hospitals, the laboratories of industry and the work supported by voluntary organizations and foundations. The breadth of NIH programs is indicated by the fact that well over four-fifths of NIH expenditures support extramural biomedical research in universities, private laboratories, and elsewhere. While the NIH campus in Bethesda (and its extension here) is the largest single biomedical research institution in the world, our intramural research programs account for only about one out of every $25 spent on such work in the United States.

The support of basic research is a responsibility of Government, for the dual reasons that it benefits the people and the economy of the nation and that there is no other substantial source for its support. The bulk of support for basic biomedical research, conducted mainly in university laboratories, will continue to come from the Federal Government, primarily through NIH. In 1981, for example, 78% of health R&D funds used by universities came from the Federal Government; 19% from university, state, local, and other nonprofit sources; and 3% from industry. While industry has an important role in the continuum of health science research, its emphasis is chiefly on development and application. The primary search for basic knowledge will continue to be conducted by universities and Federal laboratories, with Federal dollars.

We are now entering the fifth decade of the Federal-academic partnership in biomedical research. We can take a degree of encouragement in making predictions for the 1980s from the fact that the principles shaping that partnership have changed little since the years immediately after World War II. A number of issues we face in the 1980s were foreseen in the 1940s—for example, what to do about obsolescent equipment and instrumentation, patents, indirect costs, rising direct costs, and small business involvement. The Federal approach to support of health research through universities has served the national interest well through the years. The basic concept of the Federal-academic partnership was expressed in a 1945 report entitled, "Science—The Endless Frontier," written by Dr. Vannevar Bush, the President's Science Advisor (*2*). The flavor and substance of the document stand up well when viewed from the perspective of nearly 40 years. Permit me to read a few sentences from it:

> "The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge. . . . Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."

Such "discoveries in remote and unexpected fields" are the objective of the Government-university partnership. A concept expressed in the 1920s by Alfred North Whitehead characterizes our present effort. Whitehead said (*3*): "The proper function of a university is *the imaginative acquisition of knowledge*." I like to think that this concept can be applied to the function of NIH as well.

An isolated fact is interesting but not useful until imagination places it in a larger context. At that point, as Whitehead said in the same lecture (*3*), "a fact is no longer a bare fact: it is invested with all its possibilities." To be engaged in "the imaginative acquisition of knowledge" at this time is, in my opinion, the most exciting opportunity in the history of health science research. The recent flood of advances in biomedical research has justifiably led to the use of the phrase "biological revolution" to describe the present state of the life sciences. This surge of new knowledge, the result of more than three decades of vigorous public support of biomedical research, has produced outstanding opportunities for progress and has created an unprecedented potential for the application of this knowledge to the improvement of health. The barriers are coming down; biomedical science has probed the innermost secrets of living processes at the cellular and molecular levels. Let me mention just a few of these areas of high promise to be pursued in the immediate future:

First, the development of recombinant DNA technology has given us an exciting tool that allows us to transfer hereditary units from one species to another and permits bacteria to become factories for the production of substances of biological, agricultural, and medical importance. The use of this technique has already led to the synthetic production of human insulin, somatostatin and growth hormone. Recombinant DNA technology also can be used to produce large quantities of pure antigen which, in turn, can be used as vaccines for immunization against infectious agents.

Second, the development of hybridoma cell fusion technology has led to facile production of an array of monoclonal antibodies for use in exquisitely specific vaccines, diagnostic tests, and treatment for many diseases. Recently, investigators have used human lung cancer cells to prepare monoclonal antibodies that can distinguish tumor cells from normal cells. This technology may permit the detection of cancer at a very early stage. In a few instances, clinicians have been able to attach radioactive or chemotherapeutic agents to the antibodies and thereby kill cancer cells without harming surrounding healthy tissue.

Third, the past decade has seen rapid growth in our knowledge of neurobiology; we are achieving a progressively better understanding of the function of the brain and central nervous system in health and disease. The discovery of slow viruses that cause significant neurological damage has been a major advance. Methods of opening the blood-brain barrier selectively have been identified and are being investigated to allow enzyme replacement in certain genetic diseases. Progress in microsurgery has greatly improved the outlook for patients with certain neurological conditions, including brain tumors and acoustic neuroma. New diagnostic tools, including computerized axial tomography (CAT), positron emission transaxial tomography (PETT) and, most recently, nuclear magnetic resonance (NMR), allow detailed imaging of the living human brain and its functions and promise to uncover a wealth of knowledge. Work on neurotransmitters, such as L-Dopa, and neuropeptides, such as encephalins, has greatly expanded our knowledge of communication within the central nervous system. I agree with many scientists who believe that neurobiology is the frontier science of this decade.

Fourth, a major concept of cancer causation, introduced in the 1960s, continues to gain support from new sero-epidemiological evidence. This is the concept of oncogenes—genes that cause tumors. Like other genes, these serve as templates for DNA that direct the production of enzymes that, in turn, catalyze the synthesis or modification of proteins. The protein products have been called oncogenic proteins, since their action causes neoplastic transformation of cells. "Onc" genes have been detected in a wide variety of vertebrate species, including man. The oncogene concept suggests that in the course of evolution an RNA-type virus became incorporated in the germline, or genome, and exists there as a silent infection before birth. It is proposed that these genes can be activated by a myriad of environmental agents that then serve as proximate causes of cancer.

Scientific advances such as these form the deepening foundation upon which we will build important achievements and health benefits in the years ahead. They will not come quickly or easily, but there is a momentum to science that will not be denied. There is much to do. We still do not understand the fundamental processes and mechanisms of heart disease, cancer, stroke, schizophrenia, arthritis, diabetes, and other major diseases. We must set our priorities in full awareness of the enormous toll of such disorders, but also with a realistic assessment of the existing state of knowledge and the readiness for discovery in each field.

The rate of progress in the ceaseless war on disease is a function of scientific opportunity, which we now have in abundance, the imaginative insight of scientists, and available funds. We are simultaneously involved in the adventure of discovery for its own sake and in pursuit of better health for all. What a combination: satisfying work in a great humanitarian cause!

But how shall we make sure that the momentum of scientific discovery is continued? We have entered a period of financial constraint in biomedical science. The period of explosive growth of support for biomedical research of the fifties and sixties, when the NIH budget increased 20-fold in constant dollars in 13 years, is long over. The second stage rocket of the cancer, heart disease and stroke initiative has now played out. After reaching an all-time high in constant dollars in 1979, the NIH budget has leveled off, and has in the past three years declined about 12% in the same dollars. The NIH is now a mature agency competing with other Federal programs for its share of the budget. In the context of the present economy NIH has been well treated by the Administration and the Congress, but it cannot anticipate extraordinary growth in the foreseeable future. In my view, we are facing more than a temporary funding constraint in biomedical science; rather, we have entered a new steady state that, all of us, NIH and universities alike, would do well to view as the future norm. A number of painful adjustments will be necessary if we are to secure the greatest amount of the best science within our available resources. Since it may not be possible to continue all the efforts and programs we have come so passionately to cherish, we will have to set our research priorities carefully, taking into consideration a wide variety of factors: the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration. Whatever our priorities and programs, which may vary as conditions and opportunities warrant, there are certain abiding principles that will continue to guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

A second fundamental principle is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period. Incidentally, in fiscal year 1982, which ended on September 30, we managed to fund 5030 such new and competing renewal awards.

Finally, the third element of these timeless principles is that there is a continuing need to assure a supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between the continued productivity of research and the availability and replenishment of the supply of qualified investigators.

Beyond those statements of principles are certain other responsibilities that also must be considered by NIH. We must recognize a need for balance between the fundamental pursuits and other NIH program components in order to assure uninterrupted progress in all segments. Among those additional components are the following six:

- Research centers which conduct multidisciplinary research focused on specific health problems, integrate basic research with clinical application, and provide a vehicle for transferring new scientific knowledge into practice in community health care settings.
- Research resources to strengthen, enhance, and maintain the quality of the environment in which biomedical research is performed.
- Biomedical communications involving the acquisition, storage, and dissemination of information needed in research, health professional education, and the delivery of health care services.
- International research activities to facilitate the exchange of scientific information and promote collaborative research efforts.
- Clinical trials to advance knowledge concerning the prevention, diagnosis, and treatment of disease and to provide evidence of safety and efficacy of new therapy.
- Special emphasis on the prevention of disease and the promotion of health as part of a Department-wide initiative.

These, then, are the major responsibilities of NIH which must be weighed in establishing our priorities and programs for the future. But the underlying principles on which all of our work is built remain the pursuit of basic research, support of independent investigators and their ideas, and the training of future scientists.

Closer to home, here at NIEHS, major programmatic efforts as demonstrated in the poster sessions illustrate the broad nature of modern biomedical inquiry—genetic toxicology, reproductive and developmental toxicology, and health-risk estimation. Many of these areas involve research under way in other Institutes as well.

At presentations this afternoon you will hear of a study to be made of environmental factors possibly involved in renal failure. These agents include lead, cadmium, analgesics, and solvents. What, if any, is the connection with renal failure? What are its dimensions? And by what processes might it lead to pathology? You will also be told of investigations into asbestos-induced lung disease and effects of certain chemicals on the male reproductive system. Merely naming these topics of inquiry indicates the wide-ranging potential effects of environmental substances on various organ systems and the broad scope of studies on the NIEHS agenda.

Raised levels of aluminum and zinc have been associated with dementias that occasionally occur during the course of chronic renal dialysis. A possible role of aluminum has also been proposed in chronic dementia of the Alzheimer's type, but this hypothesis has prompted considerable controversy. Scientists supported by NIEHS have now confirmed findings of raised aluminum levels in the brains of Alzheimer's disease patients, and have devised a means to pinpoint the site of aluminum concentrations in the hippocampus of the brain. The question of the etiological role of aluminum, if any, remains open, but the investigation continues.

A final instance that I would like to cite concerns unexpected findings made by NIEHS scientists who were investigating effects of the estrogen DES on children of mothers who used this hormone during pregnancy. In experimental studies in rats given DES, they discovered abnormal developmental of genitalia in male offspring. Subsequently, other scientists reported findings that male offspring of DES rat "mothers" were sterile. This outcome has since also been observed in clinical practice.

These are illustrations of the sometimes surprising findings that prompt further study and, thereby, lead us closer to the answers we seek. The prospects are clearly for greater-than-ever achievement in the future; the record of the past gives us reason for confidence.

I believe that the strong and healthy partnership of NIH and the universities of this country, based on long-standing principles of cooperation in the cause of science, will serve us well in arriving at mutually agreeable and productive solutions to the problems we face.

As we confront the issues of the 1980s and beyond, we must renew our commitment in support of the overriding objectives we share—the conquest of disease and better health for all. Through our joint pursuit of the "imaginative acquisition of knowledge," I am confident that we will continue to move steadily toward realization of our goals.

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